fixed and may change over time. The model predicts that the total number of active motors on each neurofilament is relatively small and relatively independent of polymer length. Thus the motors may not be distributed uniformly along the filaments.

P457

Witnessing microtubule-based transport in the living brain: Impact of the cargo-motor receptor, amyloid precursor protein, and Alzheimer's plaques.

F.L. Chaves[1], C.S. Medina[1], X. Zhang[2], R.E. Jacobs[2], E.L. Bearer[1,3];
[1]Department of Pathology, University of New Mexico, Albuquerque, NM, [2]Beckman Institute, California Institute of Technology, Pasadena, CA, [3]Biology, California Institute of Technology, Pasadena, CA

Most amyloid precursor protein (APP)-based Alzheimer's models overexpress mutant human APP resulting in Abeta plaques. Yet the relative contribution of this elevated APP and the presence of plaques to neurodegeneration remains a big question. APP's role as a cargo-motor receptor for axonal transport suggests that overexpression might lead to increased transport. Indeed we showed that transport is increased in Down's syndrome and decreased in APP knockout mice. Hence transport may be elevated in APP overexpressors and lead to either beneficial or deleterious consequences. Here we use high field microMRI with Mn2+, an MR contrast agent useful as a track-tracer, to pose this cell biological question within the whole living brains of wildtype and Alzheimer's model mice. Injection of Mn2+ into the CA3 region of the hippocampus results in measurable transport over time. Application of 3D unbiased whole brain image analysis detects all circuitry emanating from the hippocampus. By driving APP Swe/Ind transgene expression with a tetracycline-sensitive promoter, APPSwe/Ind expression can be decoupled from the presence of plaques with doxycycline (doxy). Three groups of mice were studied: group 'A' (no doxy, +plaques, +APP); group 'B' (doxy at 8 days before sacrifice, +plaques, no APP), and group 'C' (doxy prior to conception, and stopped 8 days before sacrifice, no plaques, +APP). Images were captured before and sequentionally after Mn2+ injection into CA3 (1, 7, 25 hr). Images were aligned and analyzed by statistical parametric mapping to identify differential accumulation within the hippocampal projections. Histopathology revealed well-developed plaques in A and B, and Western blots showed human APP expressed five-fold over WT in in A and C. Our preliminary results show increased transport in A and C, with APP Swe/Ind expression when compared with B, where expression is suppressed. Cholinergic neurons in the medial septal nucleus were decreased as determined by anti-ChAT staining in Group C ($p=0.0006$ by one-way ANOVA, $n=15$). In conclusion, the effects of elevated APP expression are separable from consequences of plaque, and each may.
Supported by NIGMS P5OGM08273 and NINDS NS062184.